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(54) PROSTHETIC DEVICES HAVING ENHANCED OSTEOGENIC PROPERTIES

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Description

Background of the Invention

[0001] Regeneration of skeletal tissues is thought to be regulated by specific protein factors that are naturally present within bone matrix. When a bone is damaged, these factors stimulate cells to form new cartilage and bone tissue which replaces or repairs lost or damaged bone. Regeneration of bone is particularly important where prosthetic implants are used without bonding cement to replace diseased bone, as in hip replacement. In these cases, formation of a tight bond between the prosthesis and the existing bone is very important, and successful function depends on the interaction between the implant and the bone tissue at the interface.

[0002] Bone healing can be stimulated by one or more osteogenic proteins which can induce a developmental cascade of cellular events resulting in endochondral bone formation. Proteins stimulating bone growth have been referred to in the literature as bone morphogenic proteins, bone inductive proteins, osteogenic proteins, osteogenin or osteoinductive proteins.

[0003] U.S. 4,968,590 (November 6, 1990) discloses the purification of "substantially pure" osteogenic protein from bone, capable of inducing endochondral bone formation in a mammal when implanted in the mammal in association with a matrix, and having a half maximum activity of at least about 25 to 50 nanograms per 25 milligrams of implanted matrix. Higher activity subsequently has been shown for this protein, e.g., 0.8-1.0 ng of osteogenic protein per mg of implant matrix, as disclosed in U.S. Patent 5,011,691. This patent also disclosed a consensus DNA sequence probe useful for identifying genes encoding osteogenic proteins, and a number of human genes encoding osteogenic proteins identified using the consensus probe, including a previously unidentified gene referred to therein as "OP1" (osteogenic protein-1). The consensus probe also identified DNA sequences corresponding to sequences termed BMP-2 Class I and Class II ("BMP2" and "BMP4" respectively) and BMP3 in International Appl. No. PCT/US87/01537. The osteogenic proteins encoded by these sequences are referred to herein as "CBMP2A," "CBMP2B", and "CBMP3", respectively. U.S. 5,011,691 also defined a consensus "active region" required for osteogenic activity and described several novel biosynthetic constructs using this consensus sequence which were capable of inducing cartilage or bone formation in a mammal in association with a matrix.

[0004] These and other researchers have stated that successful implantation of the osteogenic factors for endochondral bone formation requires that the proteins be associated with a suitable carrier material or matrix which maintains the proteins at the site of application. Bone collagen particles which remain after demineralization, guanidine extraction and delipidation of pulverized bone have been used for this purpose. Many osteoinductive proteins are useful cross-species. However, demineralized, delipidated, guanidine-extracted xenogenic collagen matrices typically have inhibited bone induction *in vivo*. Sampath and Reddi (1983) *Proc. Natl. Acad. Sci. USA*, 80: 6591-6594. Recently, however, Sampath et al. have described a method for treating demineralized guanidine-extracted bone powder to create a matrix useful for xenogenic implants. *See*, U.S. 4,975,526 (December 4, 1990). Other useful matrix materials include for example, collagen; homopolymers or copolymers of glycolic acid, lactic acid, and butyric acid, including derivatives thereof; and ceramics, such as hydroxyapatite, tricalcium phosphate and other calcium phosphates. Combinations of these matrix materials also may be useful.

[0005] Orthopedic implants have traditionally been attached to natural bone using bone cement. More recently, cementless prostheses have been used, in which the portion of the prosthesis that contacts the natural bone is coated with a porous material. M. Spector, *J. Arthroplasty*, 2(2):163-176 (1987); and Cook et al., *Clin. Orthoped. and Rel. Res.*, 232: 225-243 (1988). Cementless fixation is preferred because biological fixation of the prosthesis is stronger when osseointegration is achieved. The porous coatings reportedly stimulate bone ingrowth resulting in enhanced biological fixation of the prosthesis. However, there are several problems with porous-coated prostheses. For example, careful prosthetic selection is required to obtain a close fit with the bone to ensure initial mechanical stabilization of the device, and surgical precision is required to ensure initial implant-bone contact to promote bone ingrowth. Porous coated implants have not resulted in bone ingrowth in some instances, for example, in porous coated tibial plateaus used in knee replacements. A prosthetic implant that results in significant bone ingrowth and forms a strong bond with the natural bone at the site of the joint would be very valuable.

[0006] The current state of the art for the anchoring of embedded implants such as dental implants also is unsatisfactory. Typically, dental implant fixation first requires preparing a tooth socket in the jawbone of an individual for prosthesis implantation by allowing bone ingrowth into the socket void to fill in the socket. This preparatory step alone can take several months to complete. The prosthesis then is threaded into the new bone in the socket and new bone is allowed to regrow around the threaded portion of the implant embedded in the socket. The interval between tooth extraction and prosthetic restoration therefore can take up to eight months. In addition, threading the prosthesis into bone can damage the integrity of the bone. Prosthetic dental implants that can improve osseointegration and reduce the time and effort for fixation would be advantageous.

Summary of the Invention

[0007] The present invention relates to the subject matter of the claims. The invention may find application in a method of enhancing the growth of bone at the site of implantation of a prosthesis to form a bond between the prosthesis and the existing bone. As used herein, a prosthesis is understood to describe the addition of an artificial part to supply a defect in the body. The method involves coating or otherwise contacting all or a portion of the prosthesis that will be in contact with bone with a substantially pure osteogenic protein. A prosthesis is coated with the osteogenic protein and then implanted in the individual at a site wherein the bone tissue and the surface of the prosthesis are maintained in close proximity for a time sufficient to permit enhanced bone tissue growth between the tissue and the implanted prosthesis. The osteogenic protein associated with the implanted prosthesis stimulates bone growth around the prosthesis and causes a stronger bond to form between the prosthesis and the existing bone than would form between the prosthesis and the bone in the absence of the protein.

[0008] In a preferred embodiment of the invention a prosthetic device, such as an artificial hip replacement device, e.g., a metallic device made from titanium, for example, is first coated with an osteogenic material which induces bone ingrowth. When the device is subsequently implanted into the individual, bone growth around the site of the implant is enhanced, causing a strong bond to form between the implant and the existing bone. The method results in enhanced biological fixation of the prosthesis in the body, which is particularly important for weight bearing prostheses. Prostheses defining a microporous surface structure are locked in place as bone formation occurs within the micropores. The metal or ceramic prosthesis itself defines such a structure.

[0009] The implant may have a shape defining one or more indentations to permit bone ingrowth. The indentations are preferably transverse to the longitudinal axis of the implant. In general, the longitudinal axis of the implant will be parallel to the longitudinal axis of the bone which has been treated to receive the implant. New bone grows into the indentations thereby filling them, integrates with the surface of the implant as described above, and integrates with existing bone. Thus, the prosthesis can be more tightly fixed into the orifice, and "latched" or held in place by bone growing into the indentations, and by osseointegration of new bone with the surface of the implant, both of which are stimulated by the osteogenic protein.

[0010] In a specific embodiment, a dental implant is used to replace missing teeth. The implant typically comprises a threaded portion which is fixed into the jawbone and a tooth portion configured to integrate with the rest of the patient's teeth. The implant is coated with osteogenic protein and threaded or screwed into a tooth socket in the jawbone prepared to receive it (e.g., bone has been allowed to grow into and fill the socket void.) In a particularly preferred embodiment, the socket is prepared to receive the implant by packing the void with a bone growth composition composed of osteogenic protein dispersed in a suitable carrier material. The combination of osteogenic protein and carrier is referred to herein as an "osteogenic device." The osteogenic protein promotes osseointegration of the implant into the jawbone without first requiring bone growth to fill the socket, and without requiring that the prosthesis be threaded into existing bone, which may weaken the integrity of the existing bone. Accordingly, the time interval between tooth extraction and prosthetic restoration is reduced significantly. It is anticipated that prosthetic restoration may be complete in as little time as one month. In addition, the ability of the osteogenic protein to promote osseointegration of the prosthesis will provide a superior anchor.

[0011] The invention results in enhanced biological fixation of the prosthesis. A strong bond is formed between the existing bone and the prosthesis, resulting in improved mechanical strength at the joining site. Higher attachment strength means that the prosthesis will be more secure and permanent, and therefore will be more comfortable and durable for the patient.

Brief Description of the Drawing

[0012] The sole Figure of the drawing schematically depicts a cross-sectional view of a portion of a prosthesis implanted in a femur and illustrates the latching action of bone ingrowth in accordance with an embodiment of the invention.

Detailed Description of the Invention

[0013] Described herein is a method for enhancing osseointegration between a prosthesis and natural bone in an individual at the site of implantation of the prosthesis. The method involves providing a prosthesis to a site of implantation together with substantially pure osteogenic protein such that the osteogenic protein is in contact with all or a portion of the implanted prosthesis. The protein promotes osseointegration of the prosthesis and the bone, resulting in a strong bond having improved tensile strength.

[0014] Osteogenic proteins which are useful in the present invention are described hereinafter.

[0015] The natural-sourced osteogenic protein in its mature, native form is a glycosylated dimer having an apparent

molecular weight of about 30 kDa as determined by SDS-PAGE. When reduced, the 30 kDa protein gives rise to two glycosylated peptide subunits having apparent molecular weights of about 16 kDa and 18 kDa. In the reduced state, the protein has no detectable osteogenic activity. The unglycosylated protein, which also has osteogenic activity, has an apparent molecular weight of about 27 kDa. When reduced, the 27 kDa protein gives rise to two unglycosylated polypeptides having molecular weights of about 14 kDa to 16 kDa. The recombinantly-produced osteogenic protein describes a class of dimeric proteins capable of inducing endochondral bone formation in a mammal comprising a pair of polypeptide chains, each of which has an amino acid sequence sufficiently duplicative of the sequence of the bio-synthetic constructs or COP-5 Or COP-7, (SEQ. ID NOS.3 and 4), such that said pair of polypeptide chains, when disulfide bonded to produce a dimeric species is capable of inducing endochondral bone formation in a mammal. As defined herein, "sufficiently duplicative" is understood to describe the class of proteins having endochondral bone activity as dimeric proteins implanted in a mammal in association with a matrix, each of the subunits having at least 60% amino acid sequence homology in the C-terminal cysteine-rich region with the sequence of OPS (residues 335 to 431, SEQ. ID No. 1). "Homology" is defined herein as amino acid sequence identity or conservative amino acid changes within the sequence, as defined by Dayoff, et al., Atlas of Protein Sequence and Structure; vol.5, Supp.3, pp. 345-362, (M.O. Dayoff, ed. Nat'l Biomed. Research Fdn., Washington, D.C., 1979.) Useful sequences include those comprising the C-terminal sequences of DPP (from *Drosophila*), Vgl (from *Xenopus*), Vgr-1 (from mouse), the OP1 and OP2 proteins, the CBMP2, CBMP3, and CBMP4 proteins (see U.S. Pat. No. 5,011,691 and U.S. Patent No. 5,266,683, the disclosures of both of which are hereby incorporated by reference, as well as the proteins referred to as BMP5 and BMP6 (see WO90/11366, PCT/US90/01630.) A number of these proteins also are described in WO88/00205, U.S. Patent No. 5,013,649 and WO91/18098. Table I provides a list of the preferred members of this family of osteogenic proteins.

TABLE I -

OSTEOGENIC PROTEIN SEQUENCES	
hOP1 -	DNA sequence encoding human OP1 protein (Seq. ID No. 1 or 3). Also referred to in related applications as "OP1", "hOP-1" and "OP-1".
OP1 -	Refers generically to the family of osteogenically active proteins produced by expression of part or all of the hOP1 gene. Also referred to in related applications as "OPI" and "OP-1".
hOP1-PP -	Amino acid sequence of human OP1 protein (prepro form), Seq. ID No. 1, residues 1-431. Also referred to in related applications as "OP1-PP" and "OPP".
OP1-18Ser -	Amino acid sequence of mature human OP1 protein, Seq. ID No. 1, residues 293-431. N-terminal amino acid is serine. Originally identified as migrating at 18 kDa on SDS-PAGE in COS cells. Depending on protein glycosylation pattern in different host cells, also migrates at 23kDa, 19kDa and 17kDa on SDS-PAGE. Also referred to in related applications as "OP1-18".
OPS -	Human OP1 protein species defining the conserved 6 cysteine skeleton in the active region (97 amino acids, Seq. ID No. 1, residues 335-431). "S" stands for "short".
OP7 -	Human OP1 protein species defining the conserved 7 cysteine skeleton in the active region (102 amino acids, Seq. ID No. 1, residues 330-431).
OP1-16Ser -	N-terminally truncated mature human OP1 protein species. (Seq. ID No. 1, residues 300-431). N-terminal amino acid is serine; protein migrates at 16kDa or 15kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16S".
OP1-16Leu -	N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 313-431. N-terminal amino acid is leucine; protein migrates at 16 or 15kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16L".
OP1-16Met -	N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 315-431. N-terminal amino acid is methionine; protein migrates at 16 or 15kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16M".
OP1-16A1a -	N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 316-431. N-terminal amino acid is alanine, protein migrates at 16 or 15 kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16A".
OP1-16Val -	N-terminally truncated mature human OP1 protein species, Seq. ID No. 1, residues 318-431. N-terminal amino acid is valine; protein migrates at 16 or 15 kDa on SDS-PAGE, depending on glycosylation pattern. Also referred to in related applications as "OP-16V".

TABLE I - (continued)

OSTEOGENIC PROTEIN SEQUENCES	
5	mOP1 - DNA encoding mouse OP1 protein, Seq. ID No. 8. Also referred to in related applications as "mOP-1".
	mOP1-PP - Prepro form of mouse protein, Seq. ID No. 8, residues 1-430. Also referred to in related applications as "mOP-1-PP".
	mOP1-Ser - Mature mouse OP1 protein species (Seq. ID No. 8, residues 292-430). N-terminal amino acid is serine. Also referred to in related applications as "mOP1" and "mOP-1".
10	mOP2 - DNA encoding mouse OP2 protein, Seq. ID No. 12. Also referred to in related applications as "mOP-2".
	mOP2-PP - Prepro form of mOP2 protein, Seq. ID No. 12, residues 1-399. Also referred to in related applications as "mOP-2-PP".
15	mOP2-Ala - Mature mouse OP2 protein, Seq. ID No. 12, residues 261-399. N-terminal amino acid in alanine. Also referred to in related applications as "mOP2" and "mOP-2".
	hOP2 - DNA encoding human OP2 protein, Seq. ID No. 10. Also referred to in related applications as "hOP-2".
	hOP2-PP - Prepro form of human OP2 protein, Seq. ID No. 10, res. 1-402). Also referred to in related applications as "hOP-2-PP".
20	hOP2-Ala - Possible mature human OP2 protein species: Seq. ID No. 10, residues 264-402. Also referred to in related applications as "hOP-2".
	hOP2-Pro - Possible mature human OP2 protein species: Seq. ID No. 10, residues 267-402. N-terminal amino acid is proline. Also referred to in related applications as "hOP-2P".
25	hOP2-Arg - Possible mature human OP2 protein species: Seq. ID No. 10, res. 270-402. N-terminal amino acid is arginine. Also referred to in related applications as "hOP-2R".
	hOP2-Ser - Possible mature human OP2 protein species: Seq. ID No. 10, res. 243-402. N-terminal amino acid is serine. Also referred to in related applications as "hOP-2S".
30	Vgr-1-fx C-terminal 102 amino acid residues of the murine "Vgr-1" protein (Seq. ID No. 7).
	CBMP2A C-terminal 101 amino acid residues of the human BMP2A protein. (Residues 296-396 of Seq. ID No. 14).
	CBMP2B C-terminal 101 amino acid residues of the human BMP2B protein. (Seq. ID No. 18).
	BMP3 Mature human BMP3 (partial sequence, Seq. ID No. 16. See U.S. 5,011,691 for C-terminal 102 residues, "CBMP3.")
35	BMP5-fx C-terminal 102 amino acid residues of the human BMP5 protein. (Seq ID No. 20).
	BMP6-fx C-terminal 102 amino acid residues of the human BMP6 protein. (Seq ID No. 21).
	COP5 Biosynthetic osteogenic 96 amino acid sequence (Seq. ID No. 3).
	COP7 Biosynthetic osteogenic 96 amino acid sequence (Seq. ID No. 4).
40	DPP-fx C-terminal 102 amino acid residues of the Drosophila "DPP" protein (Seq. ID No. 5).
	Vgl-fx C-terminal 102 amino acid residues of the Xenopus "Vgl" protein (Seq. ID No. 6).

45 **[0016]** The members of this family of proteins share a conserved six or seven cysteine skeleton in this region (e.g., the linear arrangement of these C-terminal cysteine residues is conserved in the different proteins.) See, for example, OPS, whose sequence defines the six cysteine skeleton, or OP7, a longer form of OP1, comprising 102 amino acids and whose sequence defines the seven cysteine skeleton.) In addition, the OP2 proteins contain an additional cysteine residue within this region.

50 **[0017]** This family of proteins includes longer forms of a given protein, as well as species and allelic variants and biosynthetic mutants, including addition and deletion mutants and variants, such as those which may alter the conserved C-terminal cysteine skeleton, provided that the alteration still allows the protein to form a dimeric species having a conformation capable of inducing bone formation in a mammal when implanted in the mammal in association with a matrix. In addition, the osteogenic proteins of this invention may include forms having varying glycosylation patterns and varying N-termini, may be naturally occurring or biosynthetically derived, and may be produced by expression of recombinant DNA in procaryotic or eucaryotic host cells. The proteins are active as a single species (e.g., as homodimers), or combined as a mixed species.

55 **[0018]** A particularly preferred embodiment of the proteins useful in the prosthetic devices of this invention includes proteins whose amino acid sequence in the cysteine-rich C-terminal domain has greater than 60% identity, and pref-

erably greater than 65% identity with the amino acid sequence of OPS.

[0019] Described herein are osteogenic proteins comprising species of polypeptide chains having the generic amino acid sequence herein referred to as "OPX" which accommodates the homologies between the various identified species of the osteogenic OP1 and OP2 proteins, and which is described by the amino acid sequence of Sequence ID No. 22.

[0020] Also described herein are nucleic acids and the osteogenically active polypeptide chains encoded by these nucleic acids which hybridize to DNA or RNA sequences encoding the active region of OP1 or OP2 under stringent hybridization conditions. As used herein, stringent hybridization conditions are defined as hybridization in 40% formamide, 5 X SSPE, 5 X Denhardt's Solution, and 0.1% SDS at 37°C overnight, and washing in 0.1 X SSPE, 0.1% SDS at 50°C.

[0021] Also described herein are nucleic acids and the osteogenically active polypeptide chains encoded by these nucleic acids which hybridize to the "pro" region of the OP1 or OP2 proteins under stringent hybridization conditions. As used herein, "osteogenically active polypeptide chains" is understood to mean those polypeptide chains which, when dimerized, produce a protein species having a conformation such that the pair of polypeptide chains is capable of inducing endochondral bone formation in a mammal when implanted in a mammal in association with a matrix or carrier.

[0022] Given the foregoing amino acid and DNA sequence information, the level of skill in the art, and the disclosures of U.S. Patent 5,011,691 and published PCT specification US 89/01469, published October 19, 1989, the disclosures of which are incorporated herein by reference, various DNAs can be constructed which encode at least the active domain of an osteogenic protein useful in this invention, and various analogs thereof (including species and allelic variants and those containing genetically engineered mutations), as well as fusion proteins, truncated forms of the mature proteins, deletion and addition mutants, and similar constructs. Moreover, DNA hybridization probes can be constructed from fragments of any of these proteins, or designed de novo from the generic sequence. These probes then can be used to screen different genomic and cDNA libraries to identify additional osteogenic proteins useful in the invention.

[0023] The DNAs can be produced by those skilled in the art using well known DNA manipulation techniques involving genomic and cDNA isolation, construction of synthetic DNA from synthesized oligonucleotides, and cassette mutagenesis techniques. 15-100mer oligonucleotides may be synthesized on a DNA synthesizer, and purified by polyacrylamide gel electrophoresis (PAGE) in Tris-Borate-EDTA buffer. The DNA then may be electroeluted from the gel. Overlapping oligomers may be phosphorylated by T4 polynucleotide kinase and ligated into larger blocks which may also be purified by PAGE.

[0024] The DNA from appropriately identified clones then can be isolated, subcloned (preferably into an expression vector), and sequenced. Plasmids containing sequences of interest then can be transfected into an appropriate host cell for protein expression and further characterization. The host may be a procaryotic or eucaryotic cell since the former's inability to glycosylate protein will not destroy the protein's morphogenic activity. Useful host cells include E. coli, Saccharomyces, the insect/baculovirus cell system, myeloma cells, CHO cells and various other mammalian cells. The vectors additionally may encode various sequences to promote correct expression of the recombinant protein, including transcription promoter and termination sequences, enhancer sequences, preferred ribosome binding site sequences, preferred mRNA leader sequences, preferred signal sequences for protein secretion, and the like.

[0025] The DNA sequence encoding the gene of interest also may be manipulated to remove potentially inhibiting sequences or to minimize unwanted secondary structure formation. The recombinant osteogenic protein also may be expressed as a fusion protein. After being translated, the protein may be purified from the cells themselves or recovered from the culture medium. All biologically active protein forms comprise dimeric species joined by disulfide bonds or otherwise associated, produced by folding and oxidizing one or more of the various recombinant polypeptide chains within an appropriate eucaryotic cell or in vitro after expression of individual subunits. A detailed description of osteogenic proteins expressed from recombinant DNA in E. coli is disclosed in U.S. Serial No. 422,699 filed October 17, 1989, the disclosure of which is incorporated herein by reference. A detailed description of osteogenic proteins expressed from recombinant DNA in numerous different mammalian cells is disclosed in U.S. Serial No. 569,920 filed August 20, 1990, the disclosure of which is hereby incorporated by reference.

[0026] Alternatively, osteogenic polypeptide chains can be synthesized chemically using conventional peptide synthesis techniques well known to those having ordinary skill in the art. For example, the proteins may be synthesized intact or in parts on a solid phase peptide synthesizer, using standard operating procedures. Completed chains then are deprotected and purified by HPLC (high pressure liquid chromatography). If the protein is synthesized in parts, the parts may be peptide bonded using standard methodologies to form the intact protein. In general, the manner in which the osteogenic proteins are made can be conventional and does not form a part of this invention.

[0027] The osteogenic proteins useful in the present invention are proteins which, when implanted in a mammalian body, induce the developmental cascade of endochondral bone formation including recruitment and proliferation of mesenchymal cells, differentiation of progenitor cells, cartilage formation, calcification of cartilage, vascular invasion, bone formation, remodeling and bone marrow differentiation. The osteopenic protein in contact with the present pros-

theses can induce the full developmental cascade of endochondral bone formation at the site of implantation essentially as it occurs in natural bone healing.

[0028] The prostheses of the invention may be stainless steel, titanium, molybdenum, cobalt, chromium and/or alloys or oxides of these metals. Such oxides typically comprise a thin, stable, adherent metal oxide surface coating. The prostheses are preferably formed from porous metals to permit infiltration of the bone, but non-porous materials also can be used. Porous metallic materials for use in prostheses are described, for example, by Spector in *J. Arthroplasty*, 2(2):163-176 (1987), and by Cook et al. in *Clin. Orthoped. and Rel. Res.*, 232:225-243 (1988), the teachings of both of which are hereby incorporated herein by reference. Metallic prostheses may be used for major bone or joint replacement and for repairing non-union fractures, for example, where the existing bone has been destroyed by disease or injury.

[0029] In a preferred embodiment of the present device and method, the prosthesis is coated with a material which enhances bone ingrowth and fixation, in addition to the protein. Materials which are useful for this purpose are bio-compatible, and preferably *in vivo* biodegradable and non-immunogenic. Such materials include, for example, collagen, hydroxyapatite, homopolymers or copolymers of glycolic acid lactic acid, and butyric acid and derivatives thereof, tricalcium phosphate or other calcium phosphates, metal oxides, (e.g., titanium oxide), and demineralized, guanidine extracted bone.

[0030] The present coated prostheses are prepared by applying a solution of the protein, and optionally, hydroxylapatite or other material to all or a portion of the prosthesis. The protein can be applied by any convenient method, for example, by dipping, brushing, immersing, spraying or freeze-drying. Hydroxylapatite is preferably applied by a plasma spraying process. The protein is preferably applied by immersing the prostheses in a solution of the protein under conditions appropriate to induce binding or precipitation of the protein from solution onto the implant. The amount of protein which is applied to the implant should be a concentration sufficient to induce endochondral bone formation when the prosthesis is implanted in the recipient. Generally a concentration in the range of at least 5µg protein per 3.4cm² surface area is sufficient for this purpose. If hydroxylapatite or other carrier material is used, it is applied to the prosthesis in an amount required to form a coating of from about 15µ to about 60µ thick. A layer about 25µ thick of hydroxylapatite has been used to improve implant fixation, as shown in the exemplification.

[0031] The prosthesis may comprise a device configured for insertion into an orifice prepared to receive the prosthesis. In this embodiment, as illustrated in the Figure, the interior of a bone 10 is hollowed out in preparation for insertion of the implant 12. The implant has a contoured surface design 14 defining plural indentations 16 to permit ingrowth of bone into the indentations. The indentations are preferably transverse to the longitudinal axis 18 of the implant. The contoured portion to be inserted in the orifice may be coated with osteogenic protein as described above. Osteogenic protein combined with a matrix material 20 is packed into the orifice with the prosthetic implant, thereby surrounding it. Stimulated by the osteogenic protein, new bone grows into the indentations 16 and becomes integrated with the surface of the implant 12 and with preexisting bone 10 as described above. Thus, the prosthesis is both mechanically and biologically fixed in place, and axial movement of the implant relative to the bone requires shearing of bone tissue. Matrix material 20 can be any of the materials described above for coating the prosthesis for enhancing bone growth and fixation, e.g., collagen, hydroxyapatite, homopolymers or copolymers of glycolic acid lactic acid, and butyric acid and derivatives thereof, tricalcium phosphate or other calcium phosphates, metal oxides and demineralized, guanidine extracted bone. Matrix materials for use with osteogenic proteins which can be used in the present embodiment are those described, for example, in U.S. Patent 5,011,691 and U.S. Patent No. 5,266,683, the teachings of which are hereby incorporated by reference.

[0032] The prosthesis illustrated in the Figure is particularly useful for dental and other implants where at least part of the prosthesis is to be embedded into bone tissue. Packing the orifice, e.g., tooth socket, with an "osteogenic device," e.g., osteogenic protein in combination with a matrix material, provides a solid material in which to embed the prosthesis without requiring that the device be threaded into existing bone. Moreover, the osteogenic protein stimulates endochondral bone formation within the socket and into and around the implant, thereby obviating the previously required step of first allowing bone ingrowth into the socket in order to provide a suitable surface into which to implant the prosthesis. Accordingly, using the method and devices of the invention, strong fixation of an implanted prosthesis may be achieved in a fraction of the time previously required, significantly shortening the time interval between tooth extraction and prosthetic restoration. In addition, this treatment may expand the use of implant therapy and enhance success rates by eliminating a surgical procedure, reducing the amount of bone lost following tooth extraction, permitting the insertion of longer implants and minimizing prosthetic compromises necessitated by alveolar ridge resorption.

[0033] The invention will be further illustrated by the following Exemplification which is not intended to be limiting in any way.

EXEMPLIFICATIONExample 1Metal Implant Fixation

[0034] Cylindrical implants 18mm in length and 5.95 ± 0.05 mm in diameter were fabricated from spherical Co-Cr-Mo particles resulting in a pore size of 250-300 μ m and a volume porosity of 38-40%. A highly crystalline, high density and low porosity hydroxylapatite (HA) coating was applied by plasma spray process to one-half of the length of each of the implants. The coating thickness was 25 μ m and did not alter the porous coating morphology.

[0035] In the initial study, three implants were treated with a partially purified bovine OP (bOP) preparation. The bOP was naturally sourced OP extracted from cortical bone and partially purified through the Sephacryl-300 HR step in the purification protocol as described in Sampath et al. (1990), *J. Biol. Chem.*, **265**: 13198-13205. 200 μ l aliquots of 4 M guanidine-HCl, 50 mM Tris-HCl, pH 7.0, containing approximately 80 μ g bOP were added to each implant in an eppendorf tube. After overnight incubation at 4°C the protein was precipitated and the implant washed with 80% ethanol. The implants were subsequently freeze dried. Two implants without bOP served as the controls.

[0036] The implants were evaluated in one skeletally mature adult mongrel dog (3-5 years old, 20-25Kg weight) using the femoral transcortical model. Standard surgical techniques were used such that the animal received the five implants in one femur. At three weeks the dog was sacrificed and the femur removed.

[0037] The harvested femur was sectioned transverse to the long axis such that each implant was isolated. Each implant was sectioned in half to yield one HA-coated and one uncoated push-out sample. Interface attachment strength was determined using a specifically designed test fixture. The implants were pushed to failure with a MTS test machine at a displacement rate of 1.27 mm/minute. After testing, all samples were prepared for standard undecalcified histologic and microradiographic analyses. The sections (4 sections from each implant) were qualitatively examined for the type and quality of tissue ingrowth, and quantitatively evaluated for % bone ingrowth with a computerized image analysis system. The mechanical and quantitative histological data is shown in Table II.

TABLE II

METAL IMPLANTS - bOP		
	3 WEEKS	
	HA-Coated	Uncoated
	Interface Shear	Strength, MPa
Control	9.70 (n=2)	3.40 (n=2)
Protein (bOP)	10.75 (n=3)	4.08 (n=3)
Percent Bone Ingrowth		
Control	42.56 (n=4)	37.82 (n=4)
Protein (bOP)	51.66 (n=4)	46.38 (n=4)

[0038] Both the mechanical and histological data suggested that bOP enhanced osseointegration of the implants. Both the HA-coated and uncoated implants showed an increase of shear strength and bone ingrowth compared with untreated controls. Moreover, the HA-coated implants appeared to show significant enhancement compared to the uncoated implant. The histological sections directly showed a greater number of cells between the metal pores.

[0039] The positive results of the initial implant study prompted a more detailed study. Twenty-seven implants were treated with a recombinant human OP1 protein. The OP1 protein was produced by transformed CHO cells. Details for the recombinant production of OP1 are disclosed in USSN 841,646, incorporated hereinabove by reference. The protein was purified to contain as the major species the protein designated OP1-18Ser (Seq. ID No. 1, residues 293-431), and about 30% truncated forms of OP1 (e.g., OP1-16Ser, OP1-16Leu, OP1-16Met, OP1-16Ala and OP1-16Val). The protein was greater than 90% pure. The implants were immersed for 30 minutes in 200 μ l 50% ethanol/0.01% TFA containing 5 μ g recombinant protein and the solution frozen in an ethanol/dry ice bath while the formulation tube was rolled. The tubes were subsequently freeze dried. Nineteen implants were also prepared by treatment with ethanol/TFA without

the OP1 protein by the same procedure.

[0040] In test implants, it was found that OP1 could be extracted from treated implants with 8M urea, 1% Tween 80, 50mM Tris, pH 8.0 and analyzed by HPLC. By this method, it was shown that all of the OP1 in the formulation tubes bound to the implant under the conditions employed. Furthermore, since the test implants were half coated with HA, additional implants were obtained to independently evaluate the binding of OP1 to each of these surfaces. Initial binding studies showed that the OP1 binds more readily to the HA than to the uncoated metal.

[0041] The implants for the second study were evaluated in skeletally mature adult mongrel dogs using the femoral transcortical model. Standard aseptic surgical techniques were used such that each animal received five implants bilaterally. Implantation periods of three weeks were used. The mechanical and quantitative histological data are shown in Table III. Three HA-coated and uncoated configurations were evaluated: controls (no treatment), precoat samples (formulated without OP1) and the OP1 samples.

TABLE III

METAL IMPLANTS - OP-1				
INTERFACE SHEAR ATTACHMENT STRENGTH, MPA			PERCENT BONE INGROWTH	
	3 Weeks:		3 Weeks:	
	HA-coated	Uncoated	HA-coated	Uncoated
Control	7.59±2.99 (n=10)	6.47±1.23 (n=10)	44.98±12.57 (n=24)	41.66±11.91 (n=24)
Precoat	7.85±3.43 (n=9)	6.49±2.20 (n=9)	40.73±16.88 (n=24)	39.14±16.18 (n=24)
Protein (hOP-1)	8.69±3.17 (n=17)	6.34±3.04 (n=17)	48.68±16.61 (n=24)	47.89±11.91 (n=24)

[0042] Mechanical testing results demonstrated enhanced attachment strength for the HA-coated samples as compared to the uncoated samples. At three weeks the greatest fixation was observed with the HA-coated implant with protein.

[0043] Histologic analysis demonstrated greater bone ingrowth for all HA-coated versus uncoated samples although the differences were not significant. The percent bone ingrowth was greatest for the HA-coated and uncoated implants with the protein present. Linear regression analysis demonstrated that attachment strength was predicted by amount of bone growth into the porous structure, presence of HA coating, and presence of protein.

Example 2

[0044] Titanium frequently is used to fabricate metal prostheses. The surface of these prostheses comprise a layer of titanium oxide. Therefore, titanium oxide itself was evaluated for its ability to serve as a carrier for OP-1 and in general for its biocompatibility with the bone formation process. The *in vivo* biological activity of implants containing a combination of titanium oxide and OP-1 (Sequence ID No. 1, residues 293-431) was examined in rat subcutaneous and intramuscular assays. Implants contained 0, 6.25, 12.5, 25 or 50 µg of OP-1 formulated onto 30 mg of titanium oxide.

[0045] Implants were formulated by a modification of the ethanol/TFA freeze-drying method. Titanium oxide pellets were milled and sieved to a particle size of 250-420 microns. 30 mg of these particles were mixed with 50 µl aliquots of 45% ethanol, 0.09% trifluoroacetic acid containing no OP-1 or various concentrations of OP-1. After 3 hours at 4 °C, the samples were frozen, freeze-dried and implanted into rats.

[0046] After 12 days *in vivo* the implants were removed and evaluated for bone formation by alkaline phosphatase specific activity, calcium content and histological evidence. The results showed that OP-1 induced the formation of bone at each concentration of OP-1 at both the subcutaneous and intramuscular implant sites. No bone formed without OP-1 added to the titanium oxide. The amount of bone as quantitated by calcium content of the implants was similar to that observed using bone collagen carriers. Therefore titanium is a useful carrier for osteogenic proteins and is biocompatible with the bone formation process.

Equivalents

[0047] One skilled in the art will be able to ascertain, using no more than routine experimentation, many equivalents to the subject matter described herein. Such equivalents are encompassed by the following claims.

SEQUENCE LISTING

[0048]

5 (1) GENERAL INFORMATION:

(i) APPLICANT:

10 (A) NAME: Creative BioMolecules, Inc.
(B) STREET: 35 South Street
(C) CITY: Hopkinton
(D) STATE: Massachusetts
(E) COUNTRY: United States
15 (F) POSTAL CODE (ZIP): 01748
(G) TELEPHONE: 1-508-435-9001
(H) TELEFAX: 1-508-435-0454
(I) TELEX:

20 (A) NAME: Stryker Biotech
(B) STREET: One Apple Hill
(C) CITY: Natick
(D) STATE: Massachusetts
(E) COUNTRY: United States
25 (F) POSTAL CODE (ZIP): 01760
(G) TELEPHONE: 1-508-653-2280
(H) TELEFAX: 1-508-653-2770
(I) TELEX:

30 (ii) TITLE OF INVENTION: PROSTHETIC DEVICES HAVING ENHANCED OSTEOGENIC PROPERTIES

(iii) NUMBER OF SEQUENCES: 22

(iv) CORRESPONDENCE ADDRESS:

35 (A) ADDRESSEE: Creative BioMolecules, Inc.
(B) STREET: 35 South Street
(C) CITY: Hopkinton
(D) STATE: MA
(E) COUNTRY: USA
40 (F) ZIP: 01748

(v) COMPUTER READABLE FORM:

45 (A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

50 (A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

55 (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: PITCHER ESQ, EDMUND R
(B) REGISTRATION NUMBER: 27,829

(C) REFERENCE/DOCKET NUMBER: STK-057

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617/248-7000

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1822 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS
- (F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 49..1341
- (C) IDENTIFICATION METHOD: experimental
- (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN" /product= "OP1" /evidence= EXPERIMENTAL /standard_name= "OP1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CCC CCT CTG GCC AGC CTG CAA GAT AGC CAT TTC CTC ACC GAC GCC GAC 441
Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala Asp
120 125 130

ATG GTC ATG AGC TTC GTC AAC CTC GTG GAA CAT GAC AAG GAA TTC TTC 489
Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe
135 140 145

10

CAC CCA CGC TAC CAC CAT CGA GAG TTC CGG TTT GAT CTT TCC AAG ATC 537
His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile
150 155 160

1.5

CCA GAA GGG GAA GCT GTC ACG GCA GCC GAA TTC CGG ATC TAC AAG GAC 585
Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp
165 170 175

20

TAC ATC CGG GAA CGC TTC GAC AAT GAG ACG TTC CGG ATC AGC GTT TAT 633
Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile Ser Val Tyr
180 185 190 195

CAG GTG CTC CAG GAG CAC TTG GGC AGG GAA TCG GAT CTC TTC CTG CTC 681
Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu Phe Leu Leu
200 205 210

25

GAC AGC CGT ACC CTC TGG GCC TCG GAG GAG GGC TGG CTG GTG TTT GAC 729
Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu Val Phe Asp
215 220 225

30

ATC ACA GCC ACC AGC AAC CAC TGG GTG GTC AAT CCG CGG CAC AAC CTG 777
Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His Asn Leu
230 235 240

GGC CTG CAG CTC TCG GTG GAG ACG CTG GAT GGG CAG AGC ATC AAC CCC 825
Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile Asn Pro
245 250 255

35

AAG TTG GCG GGC CTG ATT GGG CGG CAC GGG CCC CAG AAC AAG CAG CCC 873
Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys Gln Pro
260 265 270 275

40

TTC ATG GTG GCT TTC TTC AAG GCC ACG GAG GTC CAC TTC CGC AGC ATC 921
Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe Arg Ser Ile
280 285 290

CGG TCC ACG GGG AGC AAA CAG CGC AGC CAG AAC CGC TCC AAG ACG CCC 969
Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser Lys Thr Pro
295 300 305

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AAG AAC CAG GAA GCC CTG CGG ATG GCC AAC GTG GCA GAG AAC AGC AGC 1017
Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu Asn Ser Ser
310 315 320

50

55

5	AGC GAC CAG AGG CAG GCC TGT AAG AAG CAC GAG CTG TAT GTC AGC TTC Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe 325 330 335	1065
10	CGA GAC CTG GGC TGG CAG GAC TGG ATC ATC GCG CCT GAA GGC TAC GCC Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala 340 345 350 355	1113
15	GCC TAC TAC TGT GAG GGG GAG TGT GCC TTC CCT CTG AAC TCC TAC ATG Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met 360 365 370	1161
20	AAC GCC ACC AAC CAC GCC ATC GTG CAG ACG CTG GTC CAC TTC ATC AAC Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn 375 380 385	1209
25	CCG GAA ACG GTG CCC AAG CCC TGC TGT GCG CCC ACG CAG CTC AAT GCC Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala 390 395 400	1257
30	ATC TCC GTC CTC TAC TTC GAT GAC AGC TCC AAC GTC ATC CTG AAG AAA Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys 405 410 415	1305
35	TAC AGA AAC ATG GTG GTC CGG GCC TGT GGC TGC CAC TAGCTCCTCC Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His 420 425 430	1351
40	GAGAATTCAG ACCCTTTGGG GCCAAGTTTT TCTGGATCCT CCATTGCTCG CCTTGGCCAG GAACCAGCAG ACCAACTGCC TTTTGTGAGA CCTTCCCCTC CCTATCCCCA ACTTTAAAGG TGTGAGAGTA TTAGGAAACA TGAGCAGCAT ATGGCTTTTG ATCAGTTTTT CAGTGGCAGC ATCCAATGAA CAAGATCCTA CAAGCTGTGC AGGCAAAACC TAGCAGGAAA AAAAAACAAC GCATAAAGAA AAATGGCCGG GCCAGGTCAT TGGCTGGGAA GTCTCAGCCA TGCACGGACT CGTTTCCAGA GGTAATTATG AGCGCCTACC A TAGGCCA CCCAGCCGTG GGAGGAAGGG GGCGTGGCAA GGGGTGGGCA CATTGGTGTC TGTGCGAAAG GAAAATTGAC CCGGAAGTTC CTGTAATAAA TGTACAATA AAACGAATGA ATGAAAAAAA AAAAAAAAAA A	1411 1471 1531 1591 1651 1711 1771 1822

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 431 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala
 1 5 10
 5 Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser
 20 25 30
 Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
 35 40 45
 10 Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
 50 55 60
 Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
 65 70 75 80
 15 Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
 85 90 95
 Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
 100 105 110
 20 Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
 115 120 125
 Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys
 130 135 140
 25 Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu
 145 150 155 160
 30 Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
 165 170 175
 Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile
 180 185 190
 35 Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu
 195 200 205
 Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu
 210 215 220
 40 Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg
 225 230 235 240
 His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser
 245 250 255
 45 Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
 260 265 270
 50
 55

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
 275 280 285
 Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
 290 295 300
 Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
 305 310 315 320
 Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
 325 330 335
 Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
 340 345 350
 Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
 355 360 365
 Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
 370 375 380
 Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
 385 390 395 400
 Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile
 405 410 415
 Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
 420 425 430

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..96
- (D) OTHER INFORMATION: /note= "COP-5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asp Asp Trp Ile Val Ala
 1 5 10 15
 Pro Pro Gly Tyr Gln Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro
 20 25 30

Leu Ala Asp His Phe Asn Ser Thr Asn His Ala Val Val Gln Thr Leu
 35 40 45
 Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr
 50 55 60
 Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val
 65 70 75 80
 Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu Gly Cys Gly Cys Arg
 85 90 95

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Protein
 (B) LOCATION: 1..96
 (D) OTHER INFORMATION: /note= "COP-7"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala
 1 5 10 15
 Pro Pro Gly Tyr His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro
 20 25 30
 Leu Ala Asp His Leu Asn Ser Thr Asn His Ala Val Val Gln Thr Leu
 35 40 45
 Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr
 50 55 60
 Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val
 65 70 75 80
 Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu Gly Cys Gly Cys Arg
 85 90 95

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: DROSOPHILA MELANOGASTER

(ix) FEATURE:

- (A) NAME/KEY: Protein
 (B) LOCATION: 1..101
 (D) OTHER INFORMATION: /label= DPP-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asp
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Asp Trp Ile Val Ala Pro Leu Gly Tyr Asp Ala Tyr Tyr Cys His Gly
20      25      30
Lys Cys Pro Phe Pro Leu Ala Asp His Phe Asn Ser Thr Asn His Ala
35      40      45
Val Val Gln Thr Leu Val Asn Asn Asn Asn Pro Gly Lys Val Pro Lys
50      55      60
Ala Cys Cys Val Pro Thr Gln Leu Asp Ser Val Ala Met Leu Tyr Leu
65      70      75      80
Asn Asp Gln Ser Thr Val Val Leu Lys Asn Tyr Gln Glu Met Thr Val
85      90      95
Val Gly Cys Gly Cys Arg
100

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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: XENOPUS

(ix) FEATURE:

- (A) NAME/KEY: Protein

(B) LOCATION: 1..102

(D) OTHER INFORMATION: /label= VG1-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

5

Cys Lys Lys Arg His Leu Tyr Val Glu Phe Lys Asp Val Gly Trp Gln
 1 5 10 15
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 20 25 30
 Glu Cys Pro Tyr Pro Leu Thr Glu Ile Leu Asn Gly Ser Asn His Ala
 35 40 45
 Ile Leu Gln Thr Leu Val His Ser Ile Glu Pro Glu Asp Ile Pro Leu
 50 55 60
 Pro Cys Cys Val Pro Thr Lys Met Ser Pro Ile Ser Met Leu Phe Tyr
 65 70 75 80
 Asp Asn Asn Asp Asn Val Val Leu Arg His Tyr Glu Asn Met Ala Val
 85 90 95
 Asp Glu Cys Gly Cys Arg
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10

15

20

25

(2) INFORMATION FOR SEQ ID NO:7:

30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 102 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

40

(A) ORGANISM: MURIDAE

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..102

(D) OTHER INFORMATION: /label= VGR-1-FX

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

50

55

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 Asp Trp Ile Ile Ala Pro Xaa Gly Tyr Ala Ala Asn Tyr Cys Asp Gly
 20 25 30
 Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
 35 40 45
 Ile Val Gln Thr Leu Val His Val Met Asn Pro Glu Tyr Val Pro Lys
 50 55 60
 Pro Cys Cys Ala Pro Thr Lys Val Asn Ala Ile Ser Val Leu Tyr Phe
 65 70 75 80
 Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
 85 90 95
 Arg Ala Cys Gly Cys His
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(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1873 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: MURIDAE
- (F) TISSUE TYPE: EMBRYO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 104..1393
- (D) OTHER INFORMATION: /function="OSTEOGENIC PROTEIN"/product="MOP1"/note="MOP1 (CD-NA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

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5	CGGCGCGGGC	CCGGTGCCCC	GGATCGCGCG	TAGAGCCGGC	GCG	ATG CAC GTG CGC Met His Val Arg	115
					1		
10	TCG CTG CGC GCT GCG GCG CCA CAC AGC TTC GTG GCG CTC TGG GCG CCT						163
	Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro						
	5		10		15		20
	CTG TTC TTG CTG CGC TCC GCC CTG GCC GAT TTC AGC CTG GAC AAC GAG						211
	Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn Glu						
		25		30		35	
15	GTG CAC TCC AGC TTC ATC CAC CGG CGC CTC CGC AGC CAG GAG CGG CGG						259
	Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg Arg						
		40		45		50	
20	GAG ATG CAG CGG GAG ATC CTG TCC ATC TTA GGG TTG CCC CAT CGC CCG						307
	Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg Pro						
		55		60		65	
	CGC CCG CAC CTC CAG GGA AAG CAT AAT TCG GCG CCC ATG TTC ATG TTG						355
	Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met Leu						
		70		75		80	
25	GAC CTG TAC AAC GCC ATG GCG GTG GAG GAG AGC GGG CCG GAC GGA CAG						403
	Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly Pro Asp Gly Gln						
		85		90		95	100
30	GGC TTC TCC TAC CCC TAC AAG GCC GTC TTC AGT ACC CAG GGC CCC CCT						451
	Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly Pro Pro						
		105		110		115	
	TTA GCC AGC CTG CAG GAC AGC CAT TTC CTC ACT GAC GCC GAC ATG GTC						499
	Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala Asp Met Val						
		120		125		130	
35	ATG AGC TTC GTC AAC CTA GTG GAA CAT GAC AAA GAA TTC TTC CAC CCT						547
	Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe His Pro						
		135		140		145	
40	CGA TAC CAC CAT CGG GAG TTC CGG TTT GAT CTT TCC AAG ATC CCC GAG						595
	Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile Pro Glu						
		150		155		160	
45	GGC GAA CGG GTG ACC GCA GCC GAA TTC AGG ATC TAT AAG GAC TAC ATC						643
	Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp Tyr Ile						
		165		170		175	180
50							
55							

5	CGG Arg	GAG Glu	CGA Arg	TTT Phe	GAC Asp 185	AAC Asn	GAG Glu	ACC Thr	TTC Phe	CAG Gln 190	ATC Ile	ACA Thr	GTC Val	TAT Tyr	CAG Gln 195	GTG Val	691
	CTC Leu	CAG Gln	GAG Glu	CAC His 200	TCA Ser	GGC Gly	AGG Arg	GAG Glu	TCG Ser 205	GAC Asp	CTC Leu	TTC Phe	TTG Leu 210	CTG Leu	GAC Asp	AGC Ser	739
10	CGC Arg	ACC Thr	ATC Ile 215	TGG Trp	GCT Ala	TCT Ser	GAG Glu	GAG Glu 220	GGC Gly	TGG Trp	TTG Leu	GTG Val 225	TTT Phe	GAT Asp	ATC Ile	ACA Thr	787
15	GCC Ala	ACC Thr 230	AGC Ser	AAC Asn	CAC His	TGG Trp	GTG Val 235	GTC Val	AAC Asn	CCT Pro	CGG Arg	CAC His 240	AAC Asn	CTG Leu	GGC Gly	TTA Leu	835
	CAG Gln 245	CTC Leu	TCT Ser	GTG Val	GAG Glu 250	ACC Thr	CTG Leu	GAT Asp	GGG Gly	CAG Gln 255	AGC Ser 255	ATC Ile	AAC Asn	CCC Pro	AAG Lys	TTG Leu 260	883
20	GCA Ala	GGC Gly	CTG Leu	ATT Ile 265	GGA Gly	CGG Arg	CAT His	GGA Gly	CCC Pro 270	CAG Gln 270	AAC Asn	AAG Lys	CAA Gln	CCC Pro	TTC Phe 275	ATG Met	931
25	GTG Val	GCC Ala	TTC Phe 280	TTC Phe	AAG Lys	GCC Ala	ACG Thr	GAA Glu 285	GTC Val 285	CAT His	CTC Leu	CGT Arg	AGT Ser 290	ATC Ile 290	CGG Arg	TCC Ser	979
	ACG Thr	GGG Gly	GGC Gly 295	AAG Lys	CAG Gln	CGC Arg	AGC Ser	CAG Gln 300	AAT Asn	CGC Arg	TCC Ser	AAG Lys 305	ACG Thr 305	CCA Pro	AAG Lys	AAC Asn	1027
30	CAA Gln 310	GAG Glu	GCC Ala	CTG Leu	AGG Arg	ATG Met	GCC Ala 315	AGT Ser	GTG Val	GCA Ala	GAA Glu	AAC Asn 320	AGC Ser	AGC Ser	AGT Ser	GAC Asp	1075
35	CAG Gln 325	AGG Arg	CAG Gln	GCC Ala	TGC Cys 330	AAG Lys	AAA Lys	CAT His	GAG Glu	CTG Leu 335	TAC Tyr 335	GTC Val	AGC Ser	TTC Phe	CGA Arg	GAC Asp 340	1123
40	CTT Leu	GGC Gly	TGG Trp	CAG Gln 345	GAC Asp	TGG Trp	ATC Ile	ATT Ile	GCA Ala 350	CCT Pro 350	GAA Glu	GGC Gly	TAT Tyr	GCT Ala	GCC Ala 355	TAC Tyr	1171
	TAC Tyr	TGT Cys	GAG Glu 360	GGA Gly	GAG Glu	TGC Cys	GCC Ala	TTC Phe	CCT Pro 365	CTG Leu	AAC Asn	TCC Ser	TAC Tyr 370	ATG Met	AAC Asn	GCC Ala	1219
45	ACC Thr	AAC Asn	CAC His 375	GCC Ala	ATC Ile	GTC Val	CAG Gln 380	ACA Thr	CTG Leu 380	GTT Val	CAC His	TTC Phe 385	ATC Ile 385	AAC Asn	CCA Pro	GAC Asp	1267

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74

1.

2.

2

3

3

(D) TOPOLOGY: linear

4.

4

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Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
50 55 60

5

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
65 70 75 80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly
85 90 95

10

Pro Asp Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr
100 105 110

Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp
115 120 125

15

Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu
130 135 140

Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser
145 150 155 160

20

Lys Ile Pro Glu Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr
165 170 175

Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Gln Ile Thr
180 185 190

25

Val Tyr Gln Val Leu Gln Glu His Ser Gly Arg Glu Ser Asp Leu Phe
195 200 205

Leu Leu Asp Ser Arg Thr Ile Trp Ala Ser Glu Glu Gly Trp Leu Val
210 215 220

30

Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His
225 230 235 240

35

Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile
245 250 255

Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys
260 265 270

40

Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Leu Arg
275 280 285

Ser Ile Arg Ser Thr Gly Gly Lys Gln Arg Ser Gln Asn Arg Ser Lys
290 295 300

45

Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Ser Val Ala Glu Asn
305 310 315 320

50

Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val
325 330 335

Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly
340 345 350

55

Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser
 355 360 365
 Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe
 370 375 380
 Ile Asn Pro Asp Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu
 385 390 395 400
 Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Asp Leu
 405 410 415
 Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
 420 425 430

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1723 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
 (F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 490..1696
 (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN" /product= "hOP2-PP" /note= "hOP2 (cDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GCGCGCCGGCA GAGCAGGAGT GGCTGCAGGA GCTGTGGTTG GAGCAGGAGG TGGCACGGCA 60
 GGGCTGGAGG GCTCCCTATG AGTGGCGGAG ACGGCCAGG AGGCGCTGGA GCAACAGCTC 120
 CCACACCGCA CCAAGCGGTG GCTGCAGGAG CTCGCCATC GCCCCTGCGC TGCTCGGACC 180
 GCGGCCACAG CCGGACTGGC GGGTACGGCG GCGACAGAGG CATTGGCCGA GAGTCCCAGT 240
 CCGCAGAGTA GCGCGGCGCT CGAGGCGGTG GCGTCCCGGT CCTCTCCGTC CAGGAGCCAG 300
 GACAGGTGTC GCGCGGCGGG GCTCCAGGGA CCGCGCTGA GGCCGGCTGC CCGCCCGTCC 360
 CGCCCCGCCC CGCCGCCCCG CGCCGCCCCG GCCCAGCCTC CTTGCCGTG GGGCGTCCCC 420

	AGGCCCTGGG TCGGCCGCGG AGCCGATGCG CGCCCGCTGA GCGCCCCAGC TGAGCGCCCC	480
5	CGGCCTGCC ATG ACC GCG CTC CCC GGC CCG CTC TGG CTC CTG GGC CTG Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu 1 5 10	528
10	GCG CTA TGC GCG CTG GGC GGG GGC GGC CCC GGC CTG CGA CCC CCG CCC Ala Leu Cys Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro 15 20 25	576
15	GGC TGT CCC CAG CGA CGT CTG GGC GCG CGC GAG CGC CGG GAC GTG CAG Gly Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln 30 35 40 45	624
	CGC GAG ATC CTG GCG GTG CTC GGG CTG CCT GGG CGG CCC CGG CCC CGC Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg 50 55 60	672
20	GCG CCA CCC GCC GCC TCC CGG CTG CCC GCG TCC GCG CCG CTC TTC ATG Ala Pro Pro Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met 65 70 75	720
25	CTG GAC CTG TAC CAC GCC ATG GCC GGC GAC GAC GAC GAG GAC GGC GCG Leu Asp Leu Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala 80 85 90	768
30	CCC GCG GAG CGG CGC CTG GGC CGC GCC GAC CTG GTC ATG AGC TTC GTT Pro Ala Glu Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val 95 100 105	816
	AAC ATG GTG GAG CGA GAC CGT GCC CTG GGC CAC CAG GAG CCC CAT TGG Asn Met Val Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp 110 115 120 125	864
35	AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT GGG GAG GCG GTC Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val 130 135 140	912
40	ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC CTG CTC Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu 145 150 155	960
	AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser 160 165 170	1008
45	AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala 175 180 185	1056

50

55

	GGA	GAC	GAG	GGC	TGG	CTG	GTG	CTG	GAT	GTC	ACA	GCA	GCC	AGT	GAC	TGC	1104
5	Gly	Asp	Glu	Gly	Trp	Leu	Val	Leu	Asp	Val	Thr	Ala	Ala	Ser	Asp	Cys	
	190					195					200					205	
	TGG	TTG	CTG	AAG	CGT	CAC	AAG	GAC	CTG	GGA	CTC	CGC	CTC	TAT	GTG	GAG	1152
	Trp	Leu	Leu	Lys	Arg	His	Lys	Asp	Leu	Gly	Leu	Arg	Leu	Tyr	Val	Glu	
					210					215					220		
10	ACT	GAG	GAC	GGG	CAC	AGC	GTG	GAT	CCT	GGC	CTG	GCC	GGC	CTG	CTG	GGT	1200
	Thr	Glu	Asp	Gly	His	Ser	Val	Asp	Pro	Gly	Leu	Ala	Gly	Leu	Leu	Gly	
				225					230					235			
15	CAA	CGG	GCC	CCA	CGC	TCC	CAA	CAG	CCT	TTC	GTG	GTC	ACT	TTC	TTC	AGG	1248
	Gln	Arg	Ala	Pro	Arg	Ser	Gln	Gln	Pro	Phe	Val	Val	Thr	Phe	Phe	Arg	
			240					245					250				
20	GCC	AGT	CCG	AGT	CCC	ATC	CGC	ACC	CCT	CGG	GCA	GTG	AGG	CCA	CTG	AGG	1296
	Ala	Ser	Pro	Ser	Pro	Ile	Arg	Thr	Pro	Arg	Ala	Val	Arg	Pro	Leu	Arg	
		255				260						265					
25	AGG	AGG	CAG	CCG	AAG	AAA	AGC	AAC	GAG	CTG	CCG	CAG	GCC	AAC	CGA	CTC	1344
	Arg	Arg	Gln	Pro	Lys	Lys	Ser	Asn	Glu	Leu	Pro	Gln	Ala	Asn	Arg	Leu	
	270					275					280					285	
30	CCA	GGG	ATC	TTT	GAT	GAC	GTC	CAC	GGC	TCC	CAC	GGC	CGG	CAG	GTC	TGC	1392
	Pro	Gly	Ile	Phe	Asp	Asp	Val	His	Gly	Ser	His	Gly	Arg	Gln	Val	Cys	
					290					295					300		
35	CGT	CGG	CAC	GAG	CTC	TAC	GTC	AGC	TTC	CAG	GAC	CTC	GGC	TGG	CTG	GAC	1440
	Arg	Arg	His	Glu	Leu	Tyr	Val	Ser	Phe	Gln	Asp	Leu	Gly	Trp	Leu	Asp	
				305					310					315			
40	TGG	GTC	ATC	GCT	CCC	CAA	GGC	TAC	TCG	GCC	TAT	TAC	TGT	GAG	GGG	GAG	1488
	Trp	Val	Ile	Ala	Pro	Gln	Gly	Tyr	Ser	Ala	Tyr	Tyr	Cys	Glu	Gly	Glu	
			320				325						330				
45	TGC	TCC	TTC	CCA	CTG	GAC	TCC	TGC	ATG	AAT	GCC	ACC	AAC	CAC	GCC	ATC	1536
	Cys	Ser	Phe	Pro	Leu	Asp	Ser	Cys	Met	Asn	Ala	Thr	Asn	His	Ala	Ile	
		335					340					345					
50	CTG	CAG	TCC	CTG	GTG	CAC	CTG	ATG	AAG	CCA	AAC	GCA	GTC	CCC	AAG	GCG	1584
	Leu	Gln	Ser	Leu	Val	His	Leu	Met	Lys	Pro	Asn	Ala	Val	Pro	Lys	Ala	
						355					360					365	
55	TGC	TGT	GCA	CCC	ACC	AAG	CTG	AGC	GCC	ACC	TCT	GTG	CTC	TAC	TAT	GAC	1632
	Cys	Cys	Ala	Pro	Thr	Lys	Leu	Ser	Ala	Thr	Ser	Val	Leu	Tyr	Tyr	Asp	
					370					375					380		
60	AGC	AGC	AAC	AAC	GTC	ATC	CTG	CGC	AAA	GCC	CGC	AAC	ATG	GTG	GTC	AAG	1680
	Ser	Ser	Asn	Asn	Val	Ile	Leu										

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 402 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys
 1 5 10 15
 Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro Gly Cys Pro
 20 25 30
 Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln Arg Glu Ile
 35 40 45
 Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Pro Pro
 50 55 60
 Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu
 65 70 75 80
 Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala Pro Ala Glu
 85 90 95
 Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val
 100 105 110
 Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp Lys Glu Phe
 115 120 125
 Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala
 130 135 140
 Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu Asn Arg Thr
 145 150 155 160
 Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser Asn Arg Glu
 165 170 175
 Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp Glu
 180 185 190

5

Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys Trp Leu Leu
195 200 205

Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Glu Asp
210 215 220

10

Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala
225 230 235 240

Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg Ala Ser Pro
245 250 255

15

Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg Arg Arg Gln
260 265 270

Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu Pro Gly Ile
275 280 285

20

Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His
290 295 300

Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp Val Ile
305 310 315 320

25

Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe
325 330 335

Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser
340 345 350

30

Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala Cys Cys Ala
355 360 365

35

Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn
370 375 380

Asn Val Ile Leu Arg Lys Ala Arg Asn Met Val Val Lys Ala Cys Gly
385 390 395 400

40

Cys His

(2) INFORMATION FOR SEQ ID NO:12:

45

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1926 base pairs

(B) TYPE: nucleic acid

50

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:

55

(A) ORGANISM: MURIDAE

(F) TISSUE TYPE: EMBRYO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 93..1289

(D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN" /product= "mOP2-PP" /note= "mOP2 cDNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

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GCCAGGCACA GGTGCGCCGT CTGGTCCTCC CCGTCTGGCG TCAGCCGAGC CCGACCAGCT      60
10
ACCAGTGGAT GCGCGCCGGC TGAAAGTCCG AG ATG GCT ATG CGT CCC GGG CCA      113
                               Met Ala Met Arg Pro Gly Pro
                               1           5

CTC TGG CTA TTG GGC CTT GCT CTG TGC GCG CTG GGA GGC GGC CAC GGT      161
Leu Trp Leu Leu Gly Leu Ala Leu Cys Ala Leu Gly Gly Gly His Gly
          10          15          20

CCG CGT CCC CCG CAC ACC TGT CCC CAG CGT CGC CTG GGA GCG CGC GAG      209
Pro Arg Pro Pro His Thr Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu
          25          30          35

CGC CGC GAC ATG CAG CGT GAA ATC CTG GCG GTG CTC GGG CTA CCG GGA      257
Arg Arg Asp Met Gln Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly
          40          45          50          55

CGG CCC CGA CCC CGT GCA CAA CCC GCC GCT GCC CGG CAG CCA GCG TCC      305
Arg Pro Arg Pro Arg Ala Gln Pro Ala Ala Arg Gln Pro Ala Ser
          60          65          70

GCG CCC CTC TTC ATG TTG GAC CTA TAC CAC GCC ATG ACC GAT GAC GAC      353
Ala Pro Leu Phe Met Leu Asp Leu Tyr His Ala Met Thr Asp Asp Asp
          75          80          85

GAC GGC GGG CCA CCA CAG GCT CAC TTA GGC CGT GCC GAC CTG GTC ATG      401
Asp Gly Gly Pro Pro Gln Ala His Leu Gly Arg Ala Asp Leu Val Met
          90          95          100

AGC TTC GTC AAC ATG GTG GAA CGC GAC CGT ACC CTG GGC TAC CAG GAG      449
Ser Phe Val Asn Met Val Glu Arg Asp Arg Thr Leu Gly Tyr Gln Glu
          105          110          115

CCA CAC TGG AAG GAA TTC CAC TTT GAC CTA ACC CAG ATC CCT GCT GGG      497
Pro His Trp Lys Glu Phe His Phe Asp Leu Thr Gln Ile Pro Ala Gly
          120          125          130          135

GAG GCT GTC ACA GCT GCT GAG TTC CGG ATC TAC AAA GAA CCC AGC ACC      545
Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Glu Pro Ser Thr
          140          145          150

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5	CAC His	CCG Pro	CTC Leu	AAC Asn 155	ACA Thr	ACC Thr	CTC Leu	CAC His	ATC Ile 160	AGC Ser	ATG Met	TTC Phe	GAA Glu	GTG Val 165	GTC Val	CAA Gln	593
10	GAG Glu	CAC His	TCC Ser 170	AAC Asn	AGG Arg	GAG Glu	TCT Ser	GAC Asp 175	TTG Leu	TTC Phe	TTT Phe	TTG Leu	GAT Asp 180	CTT Leu	CAG Gln	ACG Thr	641
15	CTC Leu	CGA Arg 185	TCT Ser	GGG Gly	GAC Asp	GAG Glu	GGC Gly 190	TGG Trp	CTG Leu	GTG Val	CTG Leu	GAC Asp 195	ATC Ile	ACA Thr	GCA Ala	GCC Ala	689
20	AGT Ser 200	GAC Asp	CGA Arg	TGG Trp	CTG Leu	CTG Leu	AAC Asn 205	CAT His	CAC His	AAG Lys	GAC Asp 210	CTG Leu	GGA Gly	CTC Leu	CGC Arg	CTC Leu 215	737
25	TAT Tyr	GTG Val	GAA Glu	ACC Thr 220	GCG Ala	GAT Asp	GGG Gly	CAC His	AGC Ser	ATG Met 225	GAT Asp	CCT Pro	GGC Gly	CTG Leu 230	GCT Ala	GGT Gly	785
30	CTG Leu	CTT Leu	GGA Gly	CGA Arg 235	CAA Gln	GCA Ala	CCA Pro	CGC Arg	TCC Ser 240	AGA Arg	CAG Gln	CCT Pro	TTC Phe	ATG Met 245	GTA Val	ACC Thr	833
35	TTC Phe	TTC Phe	AGG Arg 250	GCC Ala	AGC Ser	CAG Gln	AGT Ser 255	CCT Pro	GTG Val	CGG Arg	GCC Ala	CCT Pro	CGG Arg 260	GCA Ala	GCG Ala	AGA Arg	881
40	CCA Pro	CTG Leu 265	AAG Lys	AGG Arg	AGG Arg	CAG Gln	CCA Pro 270	AAG Lys	AAA Lys	ACG Thr	AAC Asn	GAG Glu 275	CTT Leu	CCG Pro	CAC His	CCC Pro	929
45	AAC Asn 280	AAA Lys	CTC Leu	CCA Pro	GGG Gly	ATC Ile 285	TTT Phe	GAT Asp	GAT Asp	GGC Gly	CAC His 290	GGT Gly	TCC Ser	CGC Arg	GGC Gly	AGA Arg 295	977
50	GAG Glu	GTT Val	TGC Cys	CGC Arg 300	AGG Arg	CAT His	GAG Glu	CTC Leu	TAC Tyr	GTG Val 305	AGC Ser	TTC Phe	CGT Arg	GAC Asp	CTT Leu 310	GGC Gly	1025
55	TGG Trp	CTG Leu	GAC Asp 315	TGG Trp	GTC Val	ATC Ile	GCC Ala	CCC Pro	CAG Gln 320	GGC Gly	TAC Tyr	TCT Ser	GCC Ala 325	TAT Tyr	TAC Tyr	TGT Cys	1073
60	GAG Glu	GGG Gly	GAG Glu 330	TGT Cys	GCT Ala	TTC Phe	CCA Pro	CTG Leu 335	GAC Asp	TCC Ser	TGT Cys	ATG Met	AAC Asn 340	GCC Ala	ACC Thr	AAC Asn	1121
65	CAT His	GCC Ala 345	ATC Ile	TTG Leu	CAG Gln	TCT Ser	CTG Leu 350	GTG Val	CAC His	CTG Leu	ATG Met	AAG Lys 355	CCA Pro	GAT Asp	GTT Val	GTC Val	1169

(2) INFORMATION FOR SEQ ID NO:13:

(A) LENGTH: 399 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Ala Met Arg Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys
1 5 10 15

Ala Leu Gly Gly Gly His Gly Pro Arg Pro Pro His Thr Cys Pro Gln
20 25 30

5 Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Met Gln Arg Glu Ile Leu
 35 40 45
 Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Gln Pro Ala
 50 55 60
 10 Ala Ala Arg Gln Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr
 65 70 75 80
 His Ala Met Thr Asp Asp Asp Asp Gly Gly Pro Pro Gln Ala His Leu
 85 90 95
 15 Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val Glu Arg Asp
 100 105 110
 Arg Thr Leu Gly Tyr Gln Glu Pro His Trp Lys Glu Phe His Phe Asp
 115 120 125
 20 Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg
 130 135 140
 Ile Tyr Lys Glu Pro Ser Thr His Pro Leu Asn Thr Thr Leu His Ile
 145 150 155 160
 25 Ser Met Phe Glu Val Val Gln Glu His Ser Asn Arg Glu Ser Asp Leu
 165 170 175
 Phe Phe Leu Asp Leu Gln Thr Leu Arg Ser Gly Asp Glu Gly Trp Leu
 180 185 190
 30 Val Leu Asp Ile Thr Ala Ala Ser Asp Arg Trp Leu Leu Asn His His
 195 200 205
 Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Ala Asp Gly His Ser
 210 215 220
 Met Asp Pro Gly Leu Ala Gly Leu Leu Gly Arg Gln Ala Pro Arg Ser
 225 230 235 240
 40 Arg Gln Pro Phe Met Val Thr Phe Phe Arg Ala Ser Gln Ser Pro Val
 245 250 255
 Arg Ala Pro Arg Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys
 260 265 270
 Thr Asn Glu Leu Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp
 275 280 285
 50 Gly His Gly Ser Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr
 290 295 300
 Val Ser Phe Arg Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln
 305 310 315 320
 55

Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp
 325 330 335
 Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His
 340 345 350
 Leu Met Lys Pro Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys
 355 360 365
 Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile
 370 375 380
 Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His
 385 390 395

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1260 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOHO SAPIENS

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 9..1196
 (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN" /product= "BMP2A" /note= "BMP2A (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GGTCGACC ATG GTG GCC GGG ACC CGC TGT CTT CTA GCG TTG CTG CTT CCC 50
 Met Val Ala Gly Thr Arg Cys Leu Leu Ala Leu Leu Leu Pro
 1 5 10
 CAG GTC CTC CTG GGC GGC GCG GCT GGC CTC GTT CCG GAG CTG GGC CGC 98
 Gln Val Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg
 15 20 25 30

5	AGG AAG TTC GCG GCG GCG TCG TCG GGC CGC CCC TCA TCC CAG CCC TCT Arg Lys Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser 35 40 45	146
10	GAC GAG GTC CTG AGC GAG TTC GAG TTG CGG CTG CTC AGC ATG TTC GGC Asp Glu Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly 50 55 60	194
15	CTG AAA CAG AGA CCC ACC CCC AGC AGG GAC GCC GTG GTG CCC CCC TAC Leu Lys Gln Arg Pro Thr Pro Ser Arg Asp Ala Val Val Pro Pro Tyr 65 70 75	242
20	ATG CTA GAC CTG TAT CGC AGG CAC TCG GGT CAG CCG GGC TCA CCC GCC Met Leu Asp Leu Tyr Arg Arg His Ser Gly Gln Pro Gly Ser Pro Ala 80 85 90	290
25	CCA GAC CAC CGG TTG GAG AGG GCA GCC AGC CGA GCC AAC ACT GTG CGC Pro Asp His Arg Leu Glu Arg Ala Ala Ser Arg Ala Asn Thr Val Arg 95 100 105 110	338
30	AGC TTC CAC CAT GAA GAA TCT TTG GAA GAA CTA CCA GAA ACG AGT GGG Ser Phe His His Glu Glu Ser Leu Glu Glu Leu Pro Glu Thr Ser Gly 115 120 125	386
35	AAA ACA ACC CGG AGA TTC TTC TTT AAT TTA AGT TCT ATC CCC ACG GAG Lys Thr Thr Arg Arg Phe Phe Phe Asn Leu Ser Ser Ile Pro Thr Glu 130 135 140	434
40	GAG TTT ATC ACC TCA GCA GAG CTT CAG GTT TTC CGA GAA CAG ATG CAA Glu Phe Ile Thr Ser Ala Glu Leu Gln Val Phe Arg Glu Gln Met Gln 145 150 155	482
45	GAT GCT TTA GGA AAC AAT AGC AGT TTC CAT CAC CGA ATT AAT ATT TAT Asp Ala Leu Gly Asn Asn Ser Ser Phe His His Arg Ile Asn Ile Tyr 160 165 170	530
50	GAA ATC ATA AAA CCT GCA ACA GCC AAC TCG AAA TTC CCC GTG ACC AGT Glu Ile Ile Lys Pro Ala Thr Ala Asn Ser Lys Phe Pro Val Thr Ser 175 180 185 190	578
55	CTT TTG GAC ACC AGG TTG GTG AAT CAG AAT GCA AGC AGG TGG GAA AGT Leu Leu Asp Thr Arg Leu Val Asn Gln Asn Ala Ser Arg Trp Glu Ser 195 200 205	626
60	TTT GAT GTC ACC CCC GCT GTG ATG CGG TGG ACT GCA CAG GGA CAC GCC Phe Asp Val Thr Pro Ala Val Met Arg Trp Thr Ala Gln Gly His Ala 210 215 220	674
65	AAC CAT GGA TTC GTG GTG GAA GTG GCC CAC TTG GAG GAG AAA CAA GGT Asn His Gly Phe Val Val Glu Val Ala His Leu Glu Glu Lys Gln Gly 225 230 235	722

5	GTC TCC AAG AGA CAT GTT AGG ATA AGC AGG TCT TTG CAC CAA GAT GAA Val Ser Lys Arg His Val Arg Ile Ser Arg Ser Leu His Gln Asp Glu 240 245 250	770
	CAC AGC TGG TCA CAG ATA AGG CCA TTG CTA GTA ACT TTT GGC CAT GAT His Ser Trp Ser Gln Ile Arg Pro Leu Leu Val Thr Phe Gly His Asp 255 260 265 270	818
10	GGA AAA GGG CAT CCT CTC CAC AAA AGA GAA AAA CGT CAA GCC AAA CAC Gly Lys Gly His Pro Leu His Lys Arg Glu Lys Arg Gln Ala Lys His 275 280 285	866
15	AAA CAG CCG AAA CGC CTT AAG TCC AGC TGT AAG AGA CAC CCT TTG TAC Lys Gln Arg Lys Arg Leu Lys Ser Ser Cys Lys Arg His Pro Leu Tyr 290 295 300	914
	GTG GAC TTC AGT GAC GTG GGG TGG AAT GAC TGG ATT GTG GCT CCC CCG Val Asp Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro 305 310 315	962
20	GGG TAT CAC GCC TTT TAC TGC CAC GGA GAA TGC CCT TTT CCT CTG GCT Gly Tyr His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala 320 325 330	1010
25	GAT CAT CTG AAC TCC ACT AAT CAT GCC ATT GTT CAG ACG TTG GTC AAC Asp His Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn 335 340 345 350	1058
	TCT GTT AAC TCT AAG ATT CCT AAG GCA TGC TGT GTC CCG ACA GAA CTC Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu 355 360 365	1106
30	AGT GCT ATC TCG ATG CTG TAC CTT GAC GAG AAT GAA AAG GTT GTA TTA Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu 370 375 380	1154
35	AAG AAC TAT CAG GAT ATG GTT GTG GAG GGT TGT GGG TGT CGC Lys Asn Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg 385 390 395	1196
	TAGTACAGCA AAATTAAATA CATAAATATA TATATATATA TATATTTTAG AAAAAAGAAA	1256
40	AAAA	1260

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Val Ala Gly Thr Arg Cys Leu Leu Ala Leu Leu Leu Pro Gln Val
 1 5 10 15
 5 Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg Arg Lys
 20 25 30
 Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser Asp Glu
 35 40 45
 10 Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly Leu Lys
 50 55 60
 Gln Arg Pro Thr Pro Ser Arg Asp Ala Val Val Pro Pro Tyr Met Leu
 65 70 75 80
 15 Asp Leu Tyr Arg Arg His Ser Gly Gln Pro Gly Ser Pro Ala Pro Asp
 85 90 95
 His Arg Leu Glu Arg Ala Ala Ser Arg Ala Asn Thr Val Arg Ser Phe
 100 105 110
 20 His His Glu Glu Ser Leu Glu Glu Leu Pro Glu Thr Ser Gly Lys Thr
 115 120 125
 Thr Arg Arg Phe Phe Phe Asn Leu Ser Ser Ile Pro Thr Glu Glu Phe
 130 135 140
 25 Ile Thr Ser Ala Glu Leu Gln Val Phe Arg Glu Gln Met Gln Asp Ala
 145 150 155 160
 30 Leu Gly Asn Asn Ser Ser Phe His His Arg Ile Asn Ile Tyr Glu Ile
 165 170 175
 Ile Lys Pro Ala Thr Ala Asn Ser Lys Phe Pro Val Thr Ser Leu Leu
 180 185 190
 35 Asp Thr Arg Leu Val Asn Gln Asn Ala Ser Arg Trp Glu Ser Phe Asp
 195 200 205
 Val Thr Pro Ala Val Met Arg Trp Thr Ala Gln Gly His Ala Asn His
 210 215 220
 Gly Phe Val Val Glu Val Ala His Leu Glu Glu Lys Gln Gly Val Ser
 225 230 235 240
 45 Lys Arg His Val Arg Ile Ser Arg Ser Leu His Gln Asp Glu His Ser
 245 250 255

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Trp Ser Gln Ile Arg Pro Leu Leu Val Thr Phe Gly His Asp Gly Lys
 260 265 270
 Gly His Pro Leu His Lys Arg Glu Lys Arg Gln Ala Lys His Lys Gln
 275 280 285
 Arg Lys Arg Leu Lys Ser Ser Cys Lys Arg His Pro Leu Tyr Val Asp
 290 295 300
 Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr
 305 310 315 320
 His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala Asp His
 325 330 335
 Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val
 340 345 350
 Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala
 355 360 365
 Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu Lys Asn
 370 375 380
 Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg
 385 390 395

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 574 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..327
- (D) OTHER INFORMATION: /product= "MATURE hBMP3 (PARTIAL)" /note= "THIS PARTIAL SEQUENCE OF THE MATURE HUMAN BMP3 PROTEIN INCLUDES THE FIRST THREE CYSTEINES OF THE CONSERVED 7 CYSTEINE SKELETON. SEE U.S. PAT. NO. 5,011,691 FOR 102 C-TERHINAL SEQUENCE (CBMP3.)"

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 328..574

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

5	CGA GCT TCT AAA ATA GAA TAC CAG TAT AAA AAG GAT GAG GTG TGG GAG	48
	Arg Ala Ser Lys Ile Glu Tyr Gln Tyr Lys Lys Asp Glu Val Trp Glu	
	1 5 10 15	
10	GAG AGA AAG CCT TAC AAG ACC CTT CAG GGC TCA GGC CCT GAA AAG AGT	96
	Glu Arg Lys Pro Tyr Lys Thr Leu Gln Gly Ser Gly Pro Glu Lys Ser	
	20 25 30	
15	AAG AAT AAA AAG AAA CAG AGA AAG GGG CCT CAT CGG AAG AGC CAG ACG	144
	Lys Asn Lys Lys Lys Gln Arg Lys Gly Pro His Arg Lys Ser Gln Thr	
	35 40 45	
20	CTC CAA TTT GAT GAG CAG ACC CTG AAA AAG GCA AGG AGA AAG CAG TGG	192
	Leu Gln Phe Asp Glu Gln Thr Leu Lys Lys Ala Arg Arg Lys Gln Trp	
	50 55 60	
25	ATT GAA CCT CGG AAT TGC GCC AGG AGA TAC CTC AAG GTA GAC TTT GCA	240
	Ile Glu Pro Arg Asn Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala	
	65 70 75 80	
30	GAT ATT GGC TGG AGT GAA TGG ATT ATC TCC CCC AAG TCC TTT GAT GCC	288
	Asp Ile Gly Trp Ser Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala	
	85 90 95	
35	TAT TAT TGC TCT GGA GCA TGC CAG TTC CCC ATG CCA AAG GTAGCCATTG	337
	Tyr Tyr Cys Ser Gly Ala Cys Gln Phe Pro Met Pro Lys	
	100 105	
40	TTCTCTGTCC TGTACTTACT TCCTATTTCC ATTAGTAGAA AGACACATTG ACTAAGTTAG	397
	TGTGCATATA GGGGGTTTGT GTAAGTGTTT GTGTTTCCAT TTGCAAAATC CATTGGGACC	457
	CCTATTTACT ACATTCTAAA CCATAATAGG TAATATGGTT ATTCTTGGTT TCTCTTTAAT	517
	GGTTGTAAAA GTCATATGAA GTCAGTATTG GTATAAAGAA GGATATGAGA AAAAAAA	574

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 109 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Arg Ala Ser Lys Ile Glu Tyr Gln Tyr Lys Lys Asp Glu Val Trp Glu
1 5 10 15

Glu Arg Lys Pro Tyr Lys Thr Leu Gln Gly Ser Gly Pro Glu Lys Ser
 20 25 30
 Lys Asn Lys Lys Lys Gln Arg Lys Gly Pro His Arg Lys Ser Gln Thr
 35 40 45
 Leu Gln Phe Asp Glu Gln Thr Leu Lys Lys Ala Arg Arg Lys Gln Trp
 50 55 60
 Ile Glu Pro Arg Asn Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala
 65 70 75 80
 Asp Ile Gly Trp Ser Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala
 85 90 95
 Tyr Tyr Cys Ser Gly Ala Cys Gln Phe Pro Met Pro Lys
 100 105

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1788 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS
 (F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 403..1626
 (C) IDENTIFICATION METHOD: experimental
 (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN" /product= "BMP2B" /evidence= EX-
 PERIMENTAL /note= "BHP2B (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAATTCGGGG CAGAGGAGGA GGGAGGGAGG GAAGGAGCGC GGAGCCCGGC CCGGAAGCTA 60
 GGTGAGTGTG GCATCCGAGC TGAGGGACGC GAGCCTGAGA CGCCGCTGCT GCTCCGGCTG 120
 AGTATCTAGC TTGTCTCCCC GATGGGATTC CCGTCCAAGC TATCTCGAGC CTGCAGCGCC 180

	ACAGTCCCCG GCCCTCGCCC AGGTTCACTG CAACCGTTCA GAGGTCCCCA GGAGCTGCTG	240
5	CTGGCGAGCC CGCTACTGCA GGGACCTATG GAGCCATTCC GTAGTGCCAT CCCGAGCAAC	300
	GCACTGCTGC AGCTTCCCTG AGCCTTTCCA GCAAGTTTGT TCAAGATTGG CTGTCAAGAA	360
10	TCATGGACTG TTATTATATG CCTTGTTTTT TGTCAAGACA CC ATG ATT CCT GGT Met Ile Pro Gly 1	414
	AAC CGA ATG CTG ATG GTC GTT TTA TTA TGC CAA GTC CTG CTA GGA GGC Asn Arg Met Leu Met Val Val Leu Leu Cys Gln Val Leu Leu Gly Gly 5 10 15 20	462
15	GCG AGC CAT GCT AGT TTG ATA CCT GAG ACG GGG AAG AAA AAA GTC GCC Ala Ser His Ala Ser Leu Ile Pro Glu Thr Gly Lys Lys Lys Val Ala 25 30 35	510
20	GAG ATT CAG GGC CAC GCG GGA GGA CGC CGC TCA GGG CAG AGC CAT GAG Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly Gln Ser His Glu 40 45 50	558
25	CTC CTG CGG GAC TTC GAG GCG ACA CTT CTG CAG ATG TTT GGG CTG CGC Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met Phe Gly Leu Arg 55 60 65	606
	CGC CGC CCG CAG CCT AGC AAG AGT GCC GTC ATT CCG GAC TAC ATG CGG Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro Asp Tyr Met Arg 70 75 80	654
30	GAT CTT TAC CGG CTT CAG TCT GGG GAG GAG GAG GAA GAG CAG ATC CAC Asp Leu Tyr Arg Leu Gln Ser Gly Glu Glu Glu Glu Glu Gln Ile His 85 90 95 100	702
35	AGC ACT GGT CTT GAG TAT CCT GAG CGC CCG GCC AGC CGG GCC AAC ACC Ser Thr Gly Leu Glu Tyr Pro Glu Arg Pro Ala Ser Arg Ala Asn Thr 105 110 115	750
40	GTG AGG AGC TTC CAC CAC GAA GAA CAT CTG GAG AAC ATC CCA GGG ACC Val Arg Ser Phe His His Glu Glu His Leu Glu Asn Ile Pro Gly Thr 120 125 130	798
	AGT GAA AAC TCT GCT TTT CGT TTC CTC TTT AAC CTC AGC AGC ATC CCT Ser Glu Asn Ser Ala Phe Arg Phe Leu Phe Asn Leu Ser Ser Ile Pro 135 140 145	846
45	GAG AAC GAG GTG ATC TCC TCT GCA GAG CTT CGG CTC TTC CGG GAG CAG Glu Asn Glu Val Ile Ser Ser Ala Glu Leu Arg Leu Phe Arg Glu Gln 150 155 160	894

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5	GTG Val 165	GAC Asp	CAG Gln	GGC Gly	CCT Pro	GAT Asp 170	TGG Trp	GAA Glu	AGG Arg	GGC Gly	TTC Phe 175	CAC His	CGT Arg	ATA Ile	AAC Asn	ATT Ile 180	942
	TAT Tyr	GAG Glu	GTT Val	ATG Met	AAG Lys 185	CCC Pro	CCA Pro	GCA Ala	GAA Glu	GTG Val 190	GTG Val	CCT Pro	GGG Gly	CAC His	CTC Leu	ATC Ile 195	990
10	ACA Thr	CGA Arg	CTA Leu	CTG Leu 200	GAC Asp	ACG Thr	AGA Arg	CTG Leu	GTC Val 205	CAC His	CAC His	AAT Asn	GTG Val	ACA Thr 210	CGG Arg	TGG Trp	1038
15	GAA Glu	ACT Thr	TTT Phe 215	GAT Asp	GTG Val	AGC Ser	CCT Pro	GCG Ala 220	GTC Val	CTT Leu	CGC Arg	TGG Trp	ACC Thr 225	CGG Arg	GAG Glu	AAG Lys	1086
20	CAG Gln 230	CCA Pro	AAC Asn	TAT Tyr	GGG Gly	CTA Leu	GCC Ala 235	ATT Ile	GAG Glu	GTG Val	ACT Thr 240	CAC His	CTC Leu	CAT His	CAG Gln	ACT Thr	1134
	CGG Arg 245	ACC Thr	CAC His	CAG Gln	GGC Gly	CAG Gln 250	CAT His	GTC Val	AGG Arg	ATT Ile	AGC Ser 255	CGA Arg	TCG Ser	TTA Leu	CCT Pro	CAA Gln 260	1182
25	GGG Gly	AGT Ser	GGG Gly	AAT Asn	TGG Trp 265	GCC Ala	CAG Gln	CTC Leu	CGG Arg	CCC Pro 270	CTC Leu	CTG Leu	GTC Val	ACC Thr	TTT Phe 275	GGC Gly	1230
30	CAT His	GAT Asp	GGC Gly	CGG Arg	GGC Gly	CAT His	GCC Ala	TTG Leu	ACC Thr 285	CGA Arg	CGC Arg	CGG Arg	AGG Arg	GCC Ala 290	AAG Lys	CGT Arg	1278
	AGC Ser	CCT Pro	AAG Lys 295	CAT His	CAC His	TCA Ser	CAG Gln	CGG Arg 300	GCC Ala	AGG Arg	AAG Lys	AAG Lys	AAT Asn 305	AAG Lys	AAC Asn	TGC Cys	1326
35	CGG Arg 310	CGC Arg	CAC His	TCG Ser	CTC Leu	TAT Tyr	GTG Val 315	GAC Asp	TTC Phe	AGC Ser	GAT Asp	GTG Val 320	GGC Gly	TGG Trp	AAT Asn	GAC Asp	1374
40	TGG Trp 325	ATT Ile	GTG Val	GCC Ala	CCA Pro	CCA Pro	GGC Gly 330	TAC Tyr	CAG Gln	GCC Ala	TTC Phe 335	TAC Tyr	TGC Cys	CAT His	GGG Gly	GAC Asp 340	1422
	TGC Cys	CCC Pro	TTT Phe	CCA Pro	CTG Leu 345	GCT Ala	GAC Asp	CAC His	CTC Leu	AAC Asn 350	TCA Ser	ACC Thr	AAC Asn	CAT His	GCC Ala 355	ATT Ile	1470
45	GTG Val	CAG Gln	ACC Thr	CTG Leu 360	GTC Val	AAT Asn	TCT Ser	GTC Val 365	AAT Asn	TCC Ser	AGT Ser	ATC Ile	CCC Pro	AAA Lys 370	GCC Ala	TGT Cys	1518

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TGT GTG CCC ACT GAA CTG AGT GCC ATC TCC ATG CTG TAC CTG GAT GAG 1566
 Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu
 375 380 385
 TAT GAT AAG GTG GTA CTG AAA AAT TAT CAG GAG ATG GTA GTA GAG GGA 1614
 Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu Gly
 390 395 400
 TGT GGG TGC CGC TGAGATCAGG CAGTCCTTGA GGATAGACAG ATATACACAC 1666
 Cys Gly Cys Arg
 405
 ACACACACAC ACACCACATA CACCACACAC ACACGTTCCC ATCCACTCAC CCACACACTA 1726
 CACAGACTGC TTCCTTATAG CTGGACTTTT ATTTAAAAAA AAAAAAAAAA AAACCCGAAT 1786
 TC 1788

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Ile Pro Gly Asn Arg Met Leu Met Val Val Leu Leu Cys Gln Val
 1 5 10 15
 Leu Leu Gly Gly Ala Ser His Ala Ser Leu Ile Pro Glu Thr Gly Lys
 20 25 30
 Lys Lys Val Ala Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly
 35 40 45
 Gln Ser His Glu Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met
 50 55 60
 Phe Gly Leu Arg Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro
 65 70 75 80
 Asp Tyr Met Arg Asp Leu Tyr Arg Leu Gln Ser Gly Glu Glu Glu Glu
 85 90 95
 Glu Gln Ile His Ser Thr Gly Leu Glu Tyr Pro Glu Arg Pro Ala Ser
 100 105 110
 Arg Ala Asn Thr Val Arg Ser Phe His His Glu Glu His Leu Glu Asn
 115 120 125

5 Ile Pro Gly Thr Ser Glu Asn Ser Ala Phe Arg Phe Leu Phe Asn Leu
 130 135 140
 Ser Ser Ile Pro Glu Asn Glu Val Ile Ser Ser Ala Glu Leu Arg Leu
 145 150 155 160
 10 Phe Arg Glu Gln Val Asp Gln Gly Pro Asp Trp Glu Arg Gly Phe His
 165 170 175
 Arg Ile Asn Ile Tyr Glu Val Met Lys Pro Pro Ala Glu Val Val Pro
 180 185 190
 15 Gly His Leu Ile Thr Arg Leu Leu Asp Thr Arg Leu Val His His Asn
 195 200 205
 Val Thr Arg Trp Glu Thr Phe Asp Val Ser Pro Ala Val Leu Arg Trp
 210 215 220
 20 Thr Arg Glu Lys Gln Pro Asn Tyr Gly Leu Ala Ile Glu Val Thr His
 225 230 235 240
 25 Leu His Gln Thr Arg Thr His Gln Gly Gln His Val Arg Ile Ser Arg
 245 250 255
 Ser Leu Pro Gln Gly Ser Gly Asn Trp Ala Gln Leu Arg Pro Leu Leu
 260 265 270
 30 Val Thr Phe Gly His Asp Gly Arg Gly His Ala Leu Thr Arg Arg Arg
 275 280 285
 Arg Ala Lys Arg Ser Pro Lys His His Ser Gln Arg Ala Arg Lys Lys
 290 295 300
 35 Asn Lys Asn Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val
 305 310 315 320
 Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr
 325 330 335
 40 Cys His Gly Asp Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr
 340 345 350
 45 Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Ser Ile
 355 360 365
 Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu
 370 375 380
 50 Tyr Leu Asp Glu Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met
 385 390 395 400
 55

Val Val Glu Gly Cys Gly Cys Arg
405

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(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

10

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

20

(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

25

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..102
- (D) OTHER INFORMATION: /note= "BMP5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

30

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
1 5 10 15

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly
20 25 30

35

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
35 40 45

40

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys
50 55 60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65 70 75 80

45

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
85 90 95

Arg Ser Cys Gly Cys His
100

50

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

55

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..102

(D) OTHER INFORMATION: /note= "BMP6"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Cys Arg Lys His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Gln
1          5          10          15
Asp Trp Ile Ile Ala Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly
20          25          30
Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
35          40          45
Ile Val Gln Thr Leu Val His Leu Met Asn Pro Glu Tyr Val Pro Lys
50          55          60
Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65          70          75          80
Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Trp Met Val Val
85          90          95
Arg Ala Cys Gly Cys His
100

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(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 102 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..102

(D) OTHER INFORMATION: /label= OPX /note= "WHEREIN XAA AT EACH POS'N IS INDEPENDENTLY SELECTED FROM THE RESIDUES OCCURRING AT THE CORRESPONDING POS'N IN THE C-TERMINAL SEQUENCE OF HOUSE OR HUMAN OP1 OR OP2 (SEE SEQ. ID NOS. 1,8,10 AND 12.)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Xaa Xaa His Glu Leu Tyr Val Xaa Phe Xaa Asp Leu Gly Trp Xaa
 1 5 10 15
 5 Asp Trp Xaa Ile Ala Pro Xaa Gly Tyr Xaa Ala Tyr Tyr Cys Glu Gly
 20 25 30
 Glu Cys Xaa Phe Pro Leu Xaa Ser Xaa Met Asn Ala Thr Asn His Ala
 35 40 45
 10 Ile Xaa Gln Xaa Leu Val His Xaa Xaa Xaa Pro Xaa Xaa Val Pro Lys
 50 55 60
 Xaa Cys Cys Ala Pro Thr Xaa Leu Xaa Ala Xaa Ser Val Leu Tyr Xaa
 65 70 75 80
 15 Asp Xaa Ser Xaa Asn Val Xaa Leu Xaa Lys Xaa Arg Asn Met Val Val
 85 90 95
 20 Xaa Ala Cys Gly Cys His
 100

25 Claims

1. A metal or ceramic prosthesis which itself defines a microporous surface structure **characterized in that** the prosthesis is coated with a recombinantly-produced dimeric osteogenic protein comprising a pair of polypeptide chains, each of which has at least 60% amino acid sequence homology in the C-terminal cysteine-rich region with residues 335 to 431 of Seq. ID No. 1 (OPS), and wherein said pair of polypeptide chains, when disulphide bonded to produce a dimeric species, is capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix.
2. The prosthesis of claim 1 having a contoured implantable portion for insertion into an orifice and having plural indentations transverse to its longitudinal axis.
3. The prosthesis of claim 1 or claim 2 wherein the prosthesis:
 - (a) is a dental implant; or
 - (b) comprises a stainless steel, titanium, molybdenum, cobalt, chromium and/or alloys or oxides of these metals.
4. The prosthesis of any one of the preceding claims wherein the osteogenic protein is unglycosylated.
5. The prosthesis of any one of the preceding claims wherein one of the chains of said protein comprises an amino acid sequence sharing greater than 60% identity with an amino acid sequence comprising residues 335 to 431 of Seq. ID No. 1 (OPS).
6. The prosthesis of claim 5 wherein the amino acid sequence of said chain of said protein comprises an amino acid sequence sharing greater than 65% identity with an amino acid sequence comprising OPS.
7. The prosthesis of claim 6 wherein the amino acid sequence of said chain of said protein comprises residues 335-431 of OPS.
8. The prosthesis of claim 5 wherein the protein is a homodimer, wherein both chains comprise the amino acid sequence of OPS.
9. The prosthesis of claim 8 wherein both chains comprise the amino acid sequence of residues 293-431 of Seq. ID

No. 1 (OP1-18Ser).

10. The prosthesis of any one of claims 1-4 wherein the protein comprises the C-terminal sequence of DPP, Vgl, Vgr-1, OP1, OP2, CBMP2, CBMP3, CBMP4, BMP5 or BMP6.
11. The prosthesis of any one of the preceding claims for biological fixation in the body.

Patentansprüche

1. Metall- oder Keramik-Prothese, die selbst eine mikroporöse Oberflächenstruktur festlegt, **dadurch gekennzeichnet, dass** die Prothese mit einem rekombinant hergestellten, dimeren osteogenetischen Protein beschichtet ist, das ein Paar Polypeptidketten umfasst, wobei jede in dem C-terminalen, Cystein-reichen Bereich mit den Resten 335 bis 431 der Seq. ID Nr. 1 (OPS) eine Aminosäuresequenz-Homologie von mindestens 60 % aufweist, und worin das Paar von Polypeptidketten, wenn zur Bildung einer dimeren Spezies über Disulfid-Brücken verbunden, eine endochondrale Knochenbildung induzieren kann, wenn in ein Säugetier mit einer Matrix assoziiert implantiert.
2. Prothese nach Anspruch 1, welche einen nachgeformten, implantierbaren Bereich zum Einfügen in eine Öffnung und mehrere Verzahnungen transversal zu ihrer Längs-Achse aufweist.
3. Prothese nach Anspruch 1 oder Anspruch 2, worin die Prothese
 - (a) ein Zahnimplantat ist; oder
 - (b) rostfreien Stahl, Titan, Molybdän, Kobalt, Chrom und/oder Legierungen oder Oxide dieser Metalle umfasst.
4. Prothese nach einem der vorstehenden Ansprüche, worin das osteogenetische Protein nicht glykolysiert ist.
5. Prothese nach einem der vorstehenden Ansprüche, worin eine der Ketten des Proteins eine Aminosäuresequenz umfasst, die eine größer als 60%-ige Identität mit einer die Reste 335 bis 431 von Seq. ID Nr. 1 (OPS) umfassenden Aminosäuresequenz teilt.
6. Prothese nach Anspruch 5, worin die Aminosäuresequenz der Kette des Proteins eine Aminosäuresequenz umfasst, die eine größer als 65%-ige Identität mit einer OPS umfassenden Aminosäuresequenz teilt.
7. Prothese nach Anspruch 6, worin die Aminosäuresequenz der Kette des Proteins die Reste 335-431 von OPS umfasst.
8. Prothese nach Anspruch 5, worin das Protein ein Homodimer ist, worin beide Ketten die Aminosäuresequenz von OPS umfassen.
9. Prothese nach Anspruch 8, worin beide Ketten die Aminosäuresequenz der Reste 293-431 von Seq. ID Nr. 1 (OP1-18Ser) umfassen.
10. Prothese nach einem der Ansprüche 1-4, worin das Protein die C-terminale Sequenz von DPP, Vgl, Vgr-1, OP1, OP2, CBMP2, CBMP3, CBMP4, BMP5 oder BMP6 umfasst.
11. Prothese nach einem der vorstehenden Ansprüche zur biologischen Befestigung im Körper.

Revendications

1. Une prothèse en métal ou en matière céramique qui a elle-même une structure à surface microporeuse **caractérisée en ce que** la prothèse est enduite d'une protéine ostéogène dimère produite par recombinaison comprenant une paire de chaînes de polypeptides, dont chacune a une homologie d'au moins 60% de la séquence d'acides aminés dans la région riche en cystéine terminal C avec les résidus 335 à 431 de la Seq. ID No. 1 (OPS), et où cette paire de chaînes de polypeptides, lorsqu'elle est liée par disulfure pour produire une espèce dimère, est capable d'induire une formation endochondrique d'os lorsqu'elle est implantée chez un mammifère en association avec une matrice.

2. Prothèse selon la revendication 1 comportant une partie profilée implantable pour l'insertion dans un orifice et comprenant une pluralité d'indents transversaux par rapport à son axe longitudinal.
3. Prothèse selon la revendication 1 ou la revendication 2 où la prothèse :
 - (a) est un implant dentaire ; ou
 - (b) comprend un acier inoxydable, du titane, du molybdène, du cobalt, du chrome et/ou des alliages ou oxydes de ces métaux.
4. Prothèse selon l'une quelconque des revendications précédentes où la protéine ostéogène n'est pas glycosylée.
5. Prothèse selon l'une quelconque des revendications précédentes où l'une des chaînes de cette protéine comprend une séquence d'acides aminés à identité supérieure à 60% par rapport à une séquence d'acides aminés comprenant les résidus 335 à 431 de la Seq. ID No. 1 (OPS).
6. Prothèse selon la revendication 5 dans laquelle la séquence d'acides aminés de cette chaîne de cette protéine comprend une séquence d'acides aminés partageant plus de 65% d'identité avec une séquence d'acides aminés comprenant l'OPS.
7. Prothèse selon la revendication 6 dans laquelle la séquence d'acides aminés de cette chaîne de cette protéine comprend les résidus 335-431 de l'OPS.
8. Prothèse selon la revendication 5 dans laquelle la protéine est un homodimère, dans lequel les deux chaînes comprennent la séquence d'acides aminés de l'OPS.
9. Prothèse selon la revendication 8 dans laquelle les deux chaînes comprennent la séquence d'acides aminés des résidus 293-431 de la Seq. ID No. (OP1-18Ser).
10. Prothèse selon l'une quelconque des revendications 1 à 4 dans laquelle la protéine comprend la séquence terminal C de DPP, Vgl, Vgr-1, OP1, OP2, CBMP2, CBMP3, CBMP4, BMP5 ou BMP6.
11. Prothèse selon l'une quelconque des revendications précédentes pour la fixation biologique dans le corps.

